REMARKS

Upon entry of the foregoing Amendment, Claims 1-10 and 12-14 will remain pending in the application. Claims 8-9 have been withdrawn from consideration. Claims 5 and 6 have been amended; and Claim 14 has been added. Support for newly added Claim 14 can be found in the specification, at least on page 8, lines 2-13. These changes do not introduce new matter, and their entry is respectfully requested.

In the Office Action of January 7, 2010, the Examiner set forth a number of grounds for rejection. These grounds are addressed individually and in detail below.

Claims Rejections Under 35 U.S.C. § 103

Claims 1-5, 7 and 10 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Leskovar et al. (WO 89/09620 of PCT/EP89/00403, which has the English language equivalent document U.S. Patent Publication No. 2002/0094542 which is a 35 U.S.C. § 371 National stage of the priority document) (hereinafter "Leskovar"); Claims 1-5, 7 and 10 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Leskovar, in light of support by Sugiura et al. (Gann, 1982) (hereinafter "Sugiura"); Claims 1-7 and 10 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Leskovar as applied to Claims 1-5, 7 and 10, and further in view of Housmen et al. (U.S. Patent 6,200,754) (hereinafter "Housmen"); Claims 1-3, 5-7, 10, 12 and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sugiura; and Claims 1-7, 10, 12 and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sugiura as applied to Claims 1-3, 5-7, 10, 12 and 13 above, and further in view of Roberts et al. (J.Gen.Virology, 1991), (hereinafter "Roberts"). Applicants respectfully disagree.

To establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F. 2d981, 180 USPQ 580 (CCPA, 1074).

The present Claim 1 is directed to a pharmaceutical composition for cancer therapy consisting essentially of: a) at least one compound having glutaminase activity; b) at least one antineoplastic agent selected from the group consisting of platinum complexes and anthracyclines; and c) at least one of carrier substances, auxiliary substances, and pharmaceutical injection media.

In Response to Examiner's Arguments

Applicants traverse the Examiner's contention regarding the terms "conjugated" and "derivatives" related to the obviousness of the claimed invention. Furthermore, it is respectfully submitted that the use of activators of effect cells, as taught by Leskovar, is unrelated to the inventive approach of the presently claimed invention. Comparison of the present specification to the disclosure of Leskovar makes it clear that the two concepts differ fundamentally.

Anthracyclines as well as platinum complexes have been known as cytotoxic agents before Leskovar. Leskovar's approach is (a) eliminating suppressor cells by a component A in the subject, (b) preactivating lymphocytes by a component B from the subject *ex vivo*, and (c) injecting the preactivated lymphocytes into the subject, thereby treating the cancer.

To achieve this goal, Leskovar uses antibodies. To increase the effect of the antibodies a lot of different substances can be conjugated. Leskovar states (emphases added for clarity):

> [0003] The present invention relates to the field of treatment of cancer. Specifically, the present invention provides **a composition that affects the immune system** of a subject to treat the subject's cancer and a method of treating cancer with the compositions of the invention.
>
> [0011] The present invention provides a method for treating cancer in a subject, comprising: **(a) eliminating suppressor cells** in the subject, (b) **preactivating lymphocytes** from the subject **ex vivo,** and (c) injecting the preactivated lymphocytes into the subject, thereby treating the cancer.
>
> [0012] The suppressor cells can be eliminated in a specific way or can be eliminated in a non-specific way. In one embodiment, **the suppressor cells can be eliminated by contacting the suppressor cells with antibodies selected from the group consisting of (a) antibodies** specific for **CD-8** positive suppressor cells, **(b) antibodies** specific for inducer- suppressor cells,

(c) antibodies specific for transducer-sup- pressor cells, **(d) antibodies** specific for a subpopulation of radiosensitive suppressor cells, **(e) antibodies** specific for immunocompetent (pan)-T cells, (f) antibodies specific for (pan)-leukocytes, and **(g) polyclonallpolyvalent antibodies** or globulins directed against T-cells and thymocytes or lymphocytes.

[0186] The innovative drugs, ensuring the **in vivo depletion of tumor-protecting suppressor cells, as well as the re-activation of tumoricidal effector cells,** correspond to those described in detail in tumor- and AIDS-patients.

[0190] There exist a series of additional **conjugates, used per se or as a component of the novel drugs,** described here, which **show immunostimulating andlor immunotherapeutical effect** and can therefore be considered as an integral part of the therapeutical approaches, discussed above.

[0192] The principle of these novel **immunoconjugates** is the **local impoverishment** of target cells (tumor- cells, leukocyte-subpopulations) concerning the essential cell substrates."

In contrast, the presently claimed invention is completely different from Leskovar and has nothing to do with antibodies, eliminating suppressor cells, preactivating lymphocytes or immunoconjugates. The present claimed invention is to combine cytostatic compounds selected from platinum complexes and anthracyclines with at least one **compound having glutaminase activity that is independently not suitable to treat cancer**.

The Abstract of the present application states: ". . . The combined preparations comprise as active substances compounds having glutaminase activity in combination with certain antineoplastic agents. The invention concerns in particular combined preparations of compounds having glutaminase activity and cytostatic compounds."

The present specification clearly sets forth that unexpected results are the basis for the presently claimed combination of a glutamine depleting agent with a cytotoxic compound that is not a glutamine antimetabolite has antitumorgenic activity. The specification of the present application states the following:

> [0010] **It was surprisingly found that certain well-known antineoplastic agents in combination with compounds having glutaminase activity are suitable for achieving this object. The combinations act synergistically and are directly or indirectly toxic for dividing cells and can thus be used for an antineoplastic therapy. The components having glutaminase activity act as amplifiers which lower the reguired dose of antineoplastic agents and reduce the side effects as**

well as the late seguelae. Platinum complexes and, in particular, cis-platinum, oxaliplatinum, carboplatinum or derivatives thereof or anthracyclines and, in particular, doxorubicin or daunomycin or derivatives thereof are used as antineoplastic agents. (Emphasis added for clarity).

Further, compounds having glutaminase activity are defined in the application:

> [0013] In the sense of the present invention ***compounds which have glutaminase activity*** *are* understood as the proteins or enzymes: glutaminase, glutaminase-asparaginase, glutaminase analogues, derivatives and modifications thereof which either occur naturally or are produced synthetically and ***inhibit glutamine production.***" (Emphasis added for clarity).

Accordingly, the compound having glutaminase activity is used to deplete/cleave glutamine in the subject.

Therefore, it is clear that the present claimed invention is different from Leskovar, who mentions an antibody therapy which eliminates suppressor cells *ex vivo*, as recited in paragraph [0192], "such compounds include immunoconjugates, composed of target cell-recognizing ABs and enzymes, cleaving essential cell metabolites in situ/locally. This immunoconjugate class can replace or support the classical immunotoxins; thus, the eventual problems associated with the RES-toxicity of immunotoxins can be circumvented."

The person of ordinary skill in the art would not recognize any relation of an immunoconjugate of an antibody combined with an enzyme for *circumventing eventual problems associated with the RES-toxicity of immunotoxins,* as mentioned byLeskovar, and the use of a compound having glutaminase activity used to *deplete glutamine in the subject,* as claimed by the present application.

The Examiner asserts that the group of anthracyclines comprises conjugates of anthracyclines and antibodies. However, there is a clear differentiation between derivatives and conjugates in the literature, meaning that a conjugation of two molecules is not a derivative of the original molecules.

Anthracycline derivatives are described in several citations and clearly distinguished from conjugates. Gruber *et al* (The effect of new anthracycline derivatives on the induction of apoptotic processes in human neoplastic cells. Folia Histochem Cytobiol. 2004;42(2): 127-130) describe WP903 as a new anthracyline derivative that is a small molecule and not coupled to a proteinogenic substance. Further anthracyline derivatives are described by Yoon *et al.* (Pharmacokinetics of DA-125, a new anthracycline, after intravenous administration to spontaneously hypertensive rats and DOCA-salt-induced hypertensive rats. Drug Metab Dispos. 1997 Jan;25(1):66-74) and Umezawa *et al.* (Mutagenicity of aclacinomycin A and daunomycin derivatives. Cancer Res. 1978 Jun;38(6):1782-4). In each citation, the structures of the derivatives are shown and it is clear that derivatives of anthracyclines are created by substitution of functional groups with a low molecular weight.

In the "Glossary of Bioanalytical Nomenclature" of the IUPAC (page 2598), conjugates are described as "*material produced by attaching two or more substances together. Conjugates of antibody with fluorochromes, radioactive isotope, or enzymes are often used in immunoassays.*" (Emphasis added)

In United States Patent 6,271,381 entitled "Cocaine derivative, protein conjugate thereof, monoclonal antibody producing cell line, method for preparing the cell line and monoclonal antibody", Yugawa *et al.* differentiate also between a derivative and a protein conjugate thereof.

They described the following:

> "The present invention relates to a cocaine-protein conjugate for use as an antigen to produce an anti-cocaine antibody, a cocaine derivative as a starting material for the conjugate, a novel monoclonal antibody producing cell line obtained from the antigen and a monoclonal antibody produced by the cell line. The monoclonal antibody is useful in immunochemically detecting cocaine or its derivative out of blood or air with high sensitivity."

Shih *et al.* (Anthracycline immunoconjugates prepared by a site-specific linkage via an amino-dextran intermediate carrier. Cancer Res. 1991 Aug 15;51(16):4192-8) developed a site-specific linking method by which the cytotoxic anthracyclines are linked to the antibody via a bridging polymer resulting in an immunoconjugate.

Jaracz *et al.* Recent advances in tumor-targeting anticancer drug conjugates. Bioorg Med Chem. 2005 Sep 1;13(17):5043-54) describe tumor-targeting drug delivery systems consisting of a tumor recognition moiety and a cytotoxic warhead connected directly or through a suitable linker to form a conjugate.

Griffith *et al.* (Cure of SCID mice bearing human B-lymphoma xenografts by an anti-CD74 antibody-anthracycline drug conjugate. Clin Cancer Res. 2003 Dec15;9(17):6567-71) prepared Doxorubicin (dox) conjugates of the murine and humanized versions of the anti B-cell antibody LL1, targeting CD74.

Therefore, it is respectfully submitted that joining together an anthracycline and an antibody is clearly defined as a conjugate and not as a derivative. Therefore, the group of anthracyclines according to the present application comprises derivatives but not conjugates of anthracyclines.

Additionally, the conjugation of anthracyclines to a protein like an enzyme or an antibody clearly changes their mechanism of action. Several citations underline this fact.

Barabas *et al.* formed conjugates of the anthracycline Adriamycin and transferrin in order to deliver anthracyclines to transferring (TRF) receptors on the plasma membranes of human tumor cells. These TRF-ADR conjugates were found to exert more efficient cytotoxicity than the free drug. It could be confirmed that free but not conjugated ADR reached the nuclei of viable cells. These data suggest that TRF-ADR conjugates mediate cytotoxicity by a mechanism other than intercalation with nuclear DNA.

Further, Leskovar also does not show that glutaminase has an antitumor effect. Leskovar generally describes that suppressor cells can be eliminated by contacting the suppressor cells with antibodies. Leskovar also mentions that different substances could be conjugated to the antibodies to circumvent eventual problems. In paragraph [0192] Leskovar mentions compounds includes immunoconiugates, composed of target cell-recognizing ABs and enzymes, cleaving essential cell metabolites in situ/locally... This immunoconjugate-class can replace or support the classical immunotoxins; thus, the eventual problems, associated with the RES-toxicitv of immunotoxins can be circumvented." Leskovar does not mention the use of glutaminase for an antitumor effect.

Shih *et al.* describe an Anthracycline, either daunomycin or doxorubicin, that was site-specifically attached to the carbohydrate moiety of a monoclonal anticarcinoembryonic antigen antibody by using amino-dextran as the intermediate carrier. The reaction resulted in an immunoconjugate that contains approximately 20 to 25 molecules of drug per molecule of immunoglobulin G. The conjugate possessed greater antitumor activity against the subcutaneous tumor than either the free drug or an irrelevant antibody conjugate, and it was well tolerated by the animals at a much higher dose level than was the unconjugated drug.

Accordingly, these citations clear show that the properties of the anthracycline are changed when conjugating it to proteins like antibodies or receptor ligands. Anthracyclines and conjugates of anthracyclines with proteins have different properties and the behaviors of these compounds are not predictable.

The Examiner alleges that it is obvious to combine two compositions, each of which is used for the same purpose in order to form a third composition to be used for the same purpose. This implies that the described glutaminase shows antitumorigenic activity. However, it was not obvious to one skilled in the art to combine antineoplastic agents with glutaminase because the enzyme itself shows no antitumorigenic effect. As described, for

example, by McGregor *et al.* (Glutaminase enhances therapeutic effectiveness of glutamine antimetabolites against human and murine solid tumors *in vivo*. Proceedings of the American association for cancer research, Vol. 30. p. 578, 1989) and Holcenberg (Enhanced effect of an L-glutamine antagonist, L-(alphaS,5S)-alpha-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid, by Acinetobacter L-glutaminase-L-asparaginase. Cancer Treat Rep. 1979 Jun;63(6):1109-14). Table 2 in Holcenberg presents the results of treatment of BDF, female mice injected with 10^5 L1210 leukemia cells. Treatment with enzyme alone produced only non-relevant increase in survival.

The antitumor effectiveness of crystalline bacterial glutaminase-asparaginase (GA) capable of depleting glutamine and asparagine for prolonged periods was studied in combination with glutamine antimetabolites 6-diazo-5-oxo-L-norleucine (DON) and acivicin as described in McGregor *et al.* Twice weekly IP injections of GA (200 IU/kg) had no effect on Meth A sarcoma tumor growth in BALB/c mice.

With respect to the Sugiura, it describes that succinylated Acinetobacter glutaminase-asparaginase was one out of 'forty-seven substances tested for antitumor activity against the McCall rat colon adenocarcinoma." On page 207, column 2, first sentence Sugiura says "All but one of the latter showed no activity against McCall tumor." The "latter" referred to by Sugiura are mitomycin C and azaserine, which he used also in the combination shown on page 211, Table III. In Table I, "Criteria for Evaluating Tumor Inhibition" are shown. By comparing average tumor diameters of treated/control (T/C) no tumor inhibition is defined by a value of >0.36 after 3 weeks of treatment. Table II on page 210 shows clearly that the used glutaminase-asparaginase with 0.91 T/C shows one of the worst values of all 47 substances used regarding tumor inhibition. Therefore, glutaminase-asparaginase shows no tumor inhibition at all.

The Examiner asserts that it would be obvious to combine anthracycline and glutaminase, contending that they are two compounds for the same purpose (treatment of cancer).

However, it was shown in multiple publications above that glutaminase has no effect on tumor inhibition. Therefore, anthracyclines and glutaminase are two compounds not for the same purpose and it is not obvious to employ the enzyme for the treatment of cancer.

The present presently claimed invention is to combine a cytostatic compound selected from platinum complexes and anthracyclines with at least one compound having glutaminase activity. Further, as stated above, this special combination of a cytotoxic agent with a compound having glutaminase activity (and no anti-tumor effect) is novel and non-obvious.

With respect to Robert, Applicants would like to call Examiner's attention to the fact that Robert does not mention a pharmaceutical composition comprising both at least one compound having a glutaminase activity and at least one anti-neoplastic agent selected from the group consisting of platinum complexes and anthracyclines exhibiting the claimed synergistic effects as claimed.

Lastly, Housman does not cure the deficiency of Leskovar, Sugiura and Robert. Housman is cited for its teachings on mitomycin C and *cis*-platinum. Housman does not teach or suggest the synergistic effect of a compound having glutaminase activity and anthracyclines, as recited in Claim 1 of the instant application.

In view of the foregoing, Applicants respectfully submit that Leskovar, Sugiura, Housmen and Roberts, individually or in combination, do not render Claim 1 obvious because they fail to teach or suggest all the claim limitations.

Further, Applicants submit that Claims 5 and 6 merely recite that said anthracyclines and platinum compounds comprise at least one of the recited compounds, but could contain more than one of said compounds. The Examiner asserts that Claims 5 and 6 are drafted in an

open manner and that Claim 5 therefore "includes modified anthracyclines." It is respectfully pointed out that Claims 5 and 6 are dependent upon Claim 1. Base Claim 1 contains a limiting Markush group, which recites, "at least one antineoplastic agent selected from the group consisting of platinum complexes and anthracyclines" (emphasis added for clarity). Base Claim 1 is requiring that the antineoplastic agent is a platinum complex or an anthracycline. As a dependent claim, Claim 5 can NOT broaden the base claim to include anthracyclines modified by conjugation to an antibody as alleged. It is respectfully submitted that the closed language of Claim 1 drawn to an antineoplastic agent consisting of an anthracycline does not allow the claim to read upon the conjugated anthracyclines of Leskovar.

Thus, Claims 2-7, 10 and 12-14 are patentable over Leskovar, Sugiura, Housmen and Roberts because they depend from Claim 1 and recite additional patentable subject matter.

In view of the foregoing, the grounds for this rejection have been obviated and withdrawal of the rejection under 35 U.S.C. § 103, is respectfully requested.

Newly Added Claim 14

Claim 14 is directed to the pharmaceutical composition of claim 13, wherein the pharmaceutical composition has a therapeutic dose of glutaminase activity from 50-150 I.U./m^2.

In contrast, Leskovar generally describes a medicament which comprises (1) antibodies or conjugates of antibodies and cytotoxic agents (*i.e.*, component A) and (2) activators of effector cells (*i.e.*, component B).

Therefore, Leskovar does not suggest at least one compound having glutaminase activity consisting of a tetramer composed of four subunits with a molecular weight of approximately 35 KDa. Leskovar also does not suggest the synergistic effects on various tumour cell lines in tissue cultures of up to a factor of 120 as recited in Claim 14.

Sugiura, Housmen and Roberts do not cure the deficiency of Leskovar since neither Sugiura, Housmen nor Roberts mentions a pharmaceutical composition dose for cancer therapy comprised of the synergistic effects of the claimed composition of up to a factor of 120, as recited in Claim 14.

Accordingly, new Claim 14 is patentable over Leskovar Sugiura, Housmen and Roberts.

CONCLUSION

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of the application, the Examiner is invited to contact Applicants' counsel, Ping Wang, M.D. (Reg. No. 48,328), at 202.842.0217.

Respectfully submitted,

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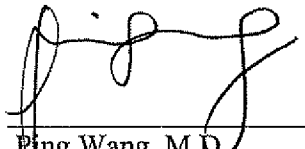

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